

## REVIEW ARTICLE

# Metabolic syndrome – dysregulation of adipose tissue endocrine function

## Metabolický syndrom – dysregulace endokrinních funkcí tukové tkáně

Kateřina Horská • Jana Kučerová • Pavel Suchý • Hana Kotolová

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### Summary

Metabolic syndrome, a condition increasing cardiovascular morbidity, mortality and risk for diabetes mellitus type 2, is currently worldwide reaching epidemic proportions. This complex disorder represents an urgent challenge for new pharmacotherapeutic strategies formulation. Pathophysiological mechanisms underlying metabolic syndrome are not completely understood, nevertheless growing evidence is supporting the hypothesis that multiple metabolic dysregulations do contribute to its development. A potential target for pharmacological intervention is considered to be dysregulation of adipose tissue endocrine/paracrine function. Specific adipokines, proteins secreted by the adipose tissue, with some pleiotropic effects, have been identified with strong association to regulation of energy metabolism, appetite, insulin signaling, tissue insulin sensitivity and the proinflammatory state related to metabolic syndrome. The aim of this paper is to provide a brief overview of endocrine/paracrine functions of the adipose tissue with regard to metabolic syndrome development and pathophysiology and particular adipokines as potential targets for innovative pharmacotherapeutic approaches.

**Keywords:** metabolic syndrome • insulin resistance • adipose tissue • adipokines

### Souhrn

Metabolický syndrom, který výrazně zvyšuje kardiovaskulární morbiditu, mortalitu a riziko rozvoje diabetes mellitus 2. typu, v současné době dosahuje epidemických proporcí. Tato komplexní porucha vyžaduje urgentní vývoj nových farmakoterapeutických řešení. Patofyziologické mechanismy vedoucí k rozvoji tohoto syndromu nejsou dosud plně objasněny, nicméně se zdá zřejmé, že k jeho rozvoji přispívá řada metabolických dysregulací. Za potenciálně slibný cíl pro vývoj nových léčiv se považuje dysregulace endokrinních a parakrinních funkcí tukové tkáně. Specifické adipokiny, což jsou proteiny secernované tukovou tkání s jistými pleiotropními účinky, jsou silně asociovány s regulací energetického metabolismu, chuti k jídlu, inzulinové signální dráhy, senzitivity periferních tkání k inzulinu a prozánětlivému stavu spojenému s metabolickým syndromem. Cílem této práce je poskytnout stručný přehled endokrinních a parakrinních funkcí tukové tkáně ve spojitosti s rozvojem metabolického syndromu, jeho patofyziologických podkladů a poukázat na některé adipokiny jako potenciální cíle pro vývoj nových farmakoterapeutických přístupů.

**Klíčová slova:** metabolický syndrom • insulinová rezistence • tuková tkáň • adipokiny

### Metabolic syndrome – definition of the concept

Metabolic syndrome is defined as a complex of interrelated risk factors for cardiovascular disease and diabetes mellitus type 2.

The concept of “metabolic syndrome” was introduced in 1988 when Gerald M. Reaven, pointing out the combination of pathophysiological signs such as insulin resistance (mainly in muscles), disruption of glycemic tolerance (diabetes), hyperinsulinism, elevated levels of VLDL lipoproteins, lowered HDL cholesterol and essential hypertension, first named this association of symptoms syndrome X<sup>1</sup>. Simultaneously, Norman

PharmDr. Bc. Hana Kotolová, PhD. (✉) • K. Horská • P. Suchý  
Ústav humánní farmakologie a toxikologie FaF  
Veterinární a Farmaceutická Univerzita  
Palackého 1-3, 612 42 Brno, ČR  
e-mail: kotolovah@vfu.cz

J. Kučerová  
Lékařská fakulta MU, Farmakologický ústav, Brno a  
Masarykova Univerzita, CEITEC –  
Středoevropský technologický institut, Brno, ČR

Kaplan published the “deadly quartet” combination of symptoms – obesity, hyperlipoproteinemia, hypertension, diabetes type 2<sup>3</sup>). The essential difference between the two first definitions was the appearance of abdominal obesity as a key symptom<sup>2-4</sup>).

Over the years, more definitions of metabolic syndrome have been proposed – the most widely respected and used nowadays ones were articulated by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) and International Diabetes Federation (IDF)<sup>5</sup>). The diagnostic criteria for metabolic syndrome were defined in 2009 by the International Diabetes Federation (IDF), American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI), American Heart Association (AHA), World Heart Federation, International Atherosclerosis Society (IAS), International Association for the Study of Obesity and World Health Association (WHO) and are as follows:

- increased waist circumference (definition varies depending on population and region) in European and Caucasian population  $\geq 80$  cm in women and  $\geq 94$  cm in men,
- triacylglycerols  $\geq 1.7$  mmol/l or current pharmacotherapy for hypertriglyceridemia
- HDL cholesterol  $< 1.0$  mmol/l in men and  $1.3$  mmol/l in women or current pharmacotherapy for low HDL levels,
- systolic blood pressure  $\geq 130$  mm Hg and/or diastolic blood pressure  $\geq 85$  mm Hg or current pharmacotherapy for already diagnosed hypertension,
- fasting glycaemia  $\geq 5.6$  mmol/l or diabetes treatment.

The presence of 3 out of the 5 abnormal findings is the basis for establishing the diagnosis and the diagnosis of metabolic syndrome is concluded when three of these factors are present without giving preference to any particular one. The thresholds for abdominal obesity – waist circumference cut points are recommended population- and country-specific<sup>6</sup>).

### **Etiology of metabolic syndrome**

The most relevant pathophysiological mechanisms underlying metabolic syndrome development include insulin resistance, increased activity of the sympathetic nervous system together with decreased functioning of adrenal gland marrow and hormonal activity of the adipose tissue itself<sup>7-9</sup>). Insulin resistance is caused by both genetic predisposition and environmental factors and in most cases is linked to obesity<sup>10</sup>). As repeatedly demonstrated in the last decades, inflammatory processes also play an important role in the pathogenesis of insulin resistance. The growing body of evidence resulted later in a complete formulation of inflammatory hypothesis of insulin resistance and metabolic syndrome<sup>11-13</sup>).

### **Role of adipose tissue and its endocrine functions in metabolic syndrome**

Development of obesity and metabolic syndrome is directly linked to the adipose tissue metabolism and endocrine activity and this function of the adipose tissue is

currently the subject of intense research. However, till 1993, adipose cells and the whole adipose tissue was regarded as a metabolically rigid part of the organism, which serves as a thermal insulation and mechanical isolation of the internal organs and stores an excess energy. The turning point came when it was discovered that adipocytes produce TNF- $\alpha$ <sup>14</sup>). Furthermore, since the first adipose tissue hormone – leptin was discovered the adipose tissue is perceived as a dynamic and plastic organ, metabolically and especially secretory (i.e. auto-, para- and endocrine) highly active, producing a large variety of mediators, so-called adipocytokines (or adipokines) which significantly modulate the number of (patho-)physiological processes and are believed to provide new treatment options for obesity and metabolic syndrome in the near future<sup>15</sup>).

Nowadays, several dozen of adipokines were identified. They have a complex effect on the metabolism of the organism, but also on many pathophysiological processes that are associated with the presence of obesity<sup>16</sup>). The expansion of adipose tissue and especially visceral fat deposits in obesity leads to dysregulation of secretion of adipokines which together with cytokines released from macrophages affect insulin sensitivity in the skeletal muscles, liver and adipose tissue itself, and are involved in the regulation of immune and inflammatory response. In accordance with the inflammatory hypothesis of metabolic syndrome this leads to the induction of full body inflammation ongoing subclinically being a risk factor in the development of atherosclerosis, diabetes type 2. Altered secretion of adipokines also leads to increased food intake and decreased energy expenditure through their effects on receptors in the hypothalamus<sup>17</sup>).

The following text describes the most important and well-studied adipokines affecting insulin signaling as a key factor for the development of insulin resistance and subsequent metabolic syndrome.

### **Adipokines important in metabolic syndrome: supporting insulin signaling**

#### ***Leptin***

The discovery of leptin was predicted long before its isolation. Almost 200 years ago, it was first suggested that the energy balance in the form of food intake is physiologically regulated against the consumption of energy. It was found that the key point for the regulation of body weight is the hypothalamus. Ventromedial nucleus of the hypothalamus (VMH) is involved in the regulation of food intake and energy expenditure, which defines the body weight. The question of how the energy can be captured by the hypothalamus gave rise to the lipostatic theory which claims that the products of fat metabolism circulating in the blood interact with the VMH. However, this theory seemed to fail at that time due to the absence of an identifiable factor in the circulation. In 1994, the positional cloning method (performed by Dr. Jeffrey Friedman’s team at Rockefeller University, USA) identified a gene for obesity – ob gene size 167 amino acids (AA), encoding the protein leptin size 16 kDa. Leptin has significant obesity promoting properties and its presence has been demonstrated in the blood of many mammalian species including human<sup>18</sup>).

Leptin has defined the newly discovered endocrine role of the adipose tissue and clarified the regulation of food intake and energy metabolism<sup>19</sup>. Leptin receptor was identified a year later<sup>20</sup>. Leptin penetrates through the blood-brain barrier and its receptors are located both centrally in the hypothalamus and in peripheral areas such as the pancreatic islets, liver, kidney, lung, skeletal muscles and bone marrow<sup>21</sup>. It has been concluded that leptin is a peripheral signal protein informing the hypothalamic center of satiety about the fat reserves of the organism, the quantity and the quality of fat tissue, which acts as a neuromediator that directly influences appetite and energy metabolism<sup>22, 23</sup>. Furthermore, leptin inhibits the neurotransmitter neuropeptide Y known as an appetite stimulator<sup>24</sup>.

Leptin is produced mainly by adipocytes and circulating levels of leptin directly correlate with the total amount of the white adipose tissue (WAT) in the organism, the size of adipocytes and the concentration of triglycerides in adipocytes. It regulates homeostasis of lipids, the elevated level of triglycerides in the blood increases the secretion of leptin that stimulates the storage of triglycerides in the adipose tissue and avoids concurrently storing triglycerides in non-fat tissues. Fat begins to accumulate in different tissues than those typical during decreased levels of leptin or in conditions of leptin resistance. Subsequently, generalized steatosis can be manifested and lipotoxicity of pancreatic  $\beta$ -cells and skeletal muscle leads to the development of insulin resistance<sup>25</sup>.

Administration of recombinant leptin to the central nervous system leads to decreased food intake and body weight in leptin-deficient mice. Peripheral administration leads to a similar effect only after administration of very high doses. However, administration of leptin in subjects with simple obesity has no effect because these individuals have increased leptinaemia and are presumed to suffer leptin resistance<sup>26</sup>.

### **Adiponectin**

Adiponectin was discovered in 1995 in mice and a year later it was described in humans and named APM1<sup>27</sup>. Adiponectin is produced mainly by mature adipocytes and its plasma levels are several order higher than that those of other proteohormones, e.g. leptin, and are higher in women than in men. Adiponectin can be found in several polymer isoforms, with the high molecular weight form being the most active one associated with most of peripheral metabolic effects<sup>28</sup>. To date, several receptors for adiponectin that are involved in the effects of adiponectin have been identified; adiponectin receptors – AdipoR1 (skeletal muscle, brain, kidney, heart, liver, lungs, spleen and testes) and AdipoR2 (liver, brain) are the basic ones<sup>29</sup>. Expression of adiponectin is regulated by multiple hormonal and neural pathways: it is increased by insulin and insulin-like growth factor 1 but at the same time an opposite effect is observed for TNF- $\alpha$ , angiotensin II and activation of the sympathetic system<sup>28</sup>. Hypertrophy of adipocytes induced by a high-fat diet causes a reduction in the production and secretion of adiponectin. Abnormal food intake and eating behavior in patients with excessive food intake lead to changes in the plasma level of adiponectin<sup>30</sup>. Plasma concentrations of

adiponectin correlate negatively with the body-mass index (BMI), level of triacylglycerols (TAG), glycaemia, fasting insulinemia and other markers of insulin resistance. Elevated plasma levels of adiponectin were found in slim people and even higher in malnourished patients, but are reduced in obese individuals<sup>31</sup>.

Adiponectin levels associated with insulin resistance are low due to obesity or lipodystrophy and administration of adiponectin under these conditions improves metabolic parameters. Conversely, adiponectin levels are increased if it improves insulin sensitivity, which occurs after weight reduction or treatment of insulin-sensitizing agents<sup>28, 31, 32</sup>. Reduction of adiponectin by pro-inflammatory cytokines (such as TNF- $\alpha$ ) is one of the possible pathophysiological mechanisms responsible for the decrease in the levels of this hormone in obesity<sup>33</sup>.

Adiponectin has a wide range of effects, including antidiabetic, anti-inflammatory and antisclerotic effects. It is involved in the regulation of metabolism of carbohydrates and lipids, increases utilization and transport of free fatty acids into the tissues and inhibits gluconeogenesis in the liver. These metabolic and insulin sensitizing effects are mediated by activation of AMPK signalization that is known to be impaired in obesity<sup>17</sup>. Adiponectin significantly affects the function of insulin and plays an important role in energetic homeostasis of the organism, causes a decrease in body weight without affecting food intake. It is believed that it also directly influences the regulation of appetite and weight control. It was shown that adiponectin acts in hypothalamus in *nucleus arcuatus* as an appetite stimulator and lowers energy expenditure<sup>34</sup>.

The adiponectin system is therefore a promising target for the development of innovative pharmacotherapy for the treatment and prevention of obesity and diabetes through direct influence on the metabolism of lipids and glucose<sup>32, 35</sup>.

### **Visfatin**

Visfatin was described in 2005 as adipokine expressed predominantly in the visceral adipose tissue<sup>36</sup>. Surprisingly, its mRNA encodes a protein which has been known long before as an immunomodulatory cytokine, pre-B cell colony-enhancing factor – PBEF<sup>37</sup>. Its importance in regulating the metabolism of lipids and carbohydrates mainly lies in the ability to bind to the insulin receptor and to activate the insulin signaling cascade supporting the effects of insulin, stimulating lipogenesis and glucose uptake into cells. Plasma level of visfatin is increased in patients with diabetes of both type 1 and 2; therefore, it is probably associated with impaired B-cell functioning<sup>38</sup>. Potential regulatory element in secretion of visfatin appears to be both glucose and insulin. The hyperglycemia leads to elevation of visfatin levels but the hyperglycemia in the presence of insulin is associated with no increase. Thus, available data suggest that the adipose tissue as a natural source of visfatin may regulate the function of B-cells<sup>25</sup>.

Visfatin plays a role in the regulation of lipid and carbohydrate metabolism mainly through its binding to the insulin receptor and activation of the insulin signaling cascade. Visfatin mediates the additive insulinomimetic

effect, increases glucose transport in myocytes, lipogenesis and differentiation of adipocytes and reduces glucose production in hepatocytes. Furthermore, it also promotes the differentiation of adipocytes and lipogenesis in the visceral adipose tissue resulting in the extending of the deposit ability of visceral fat and the possibility of absorbing larger amounts of lipids, which might otherwise interfere with the metabolism of other insulin-dependent tissues<sup>39</sup>).

### **Omentin**

Omentin is a specific protein abundant in the stroma of supportive blood vessels of the visceral adipose tissue. It has a positive effect on glucose uptake by adipocytes in a similar way as visfatin, increases the sensitivity of cells to insulin, but does not show the insulinomimetic effects. The content of plasma omentin-1, the major circulating isoform, was compared with the degree of obesity and insulin resistance and was established as a homeostatic model for prediction of a positive correlation with adiponectin and concentration of HDL-cholesterol<sup>25, 40</sup>. Omentin-1 seems to correlate positively also with adipose tissue mass and glucose homeostasis<sup>41</sup> and appears to be regulated by glucose and insulin<sup>42</sup>.

Recent evidence suggests a strong part for omentin-1 in the appetite regulation. Chronic administration of omentin-1 was shown to promote food intake and increase in body weight in rats. This effect might be at least partly related to direct central action of omentin-1 on hypothalamus which consists in lowered cocaine and amphetamine-regulated transcript (CART) and corticotrophin releasing hormone (CRH) gene expression. Besides this, omentin-1 dose-dependently increases hypothalamic synthesis and release of norepinephrine which can be reversed by leptin. However, there are so far some contradictory data recorded when omentin-1 was administered centrally and peripherally. This suggests that the observed orexigenic effect of omentin-1 might involve also some peripheral mechanisms<sup>43</sup>.

### **Vaspin**

Vaspin (visceral adipose-specific serpin) was identified as the product of both the visceral and subcutaneous adipose tissue. It is structurally one of the members of the family of serine protease inhibitors, called serpin. It is produced by the adipose tissue and exhibits 40 % of homology with  $\alpha$ 1-antitrypsin<sup>44</sup>). Vaspin may also play a role in obesity and associated disorders. The extent of its significance in human metabolism still remains unclear. Its secretion is shown to be impaired in the course of diabetes and weight loss<sup>45</sup>).

Elevated vaspin serum concentrations and mRNA expression in the human adipose tissue were found to be associated with obesity, insulin resistance, and type 2 diabetes in humans. However, the exact mechanisms are not entirely understood<sup>46</sup>). Vaspin serum concentrations are related to food intake and show diurnal variation. The peak concentrations were found early morning before breakfast falling to basal levels 2 h after breakfast with an evident preprandial rise and a postprandial fall at other meals. Importantly, diurnal pattern of serum vaspin levels was reciprocal to that of insulin and glucose suggesting a role for vaspin in metabolic regulation<sup>47</sup>). However,

further studies need to elucidate vaspin role in appetite regulation and metabolism as it might be only a biomarker for body weight related changes of insulin sensitivity but still, there is a possibility it is implicated in the regulation of glucose homeostasis<sup>48</sup>).

### **Adipokines important in metabolic syndrome: suppressing insulin signaling**

#### **Resistin**

Resistin was first described in 2001 as a link between obesity and diabetes<sup>49</sup>). Resistin is also known as the adipose tissue-specific secretory factor (ADSF) or C/EBP-epsilon-regulated myeloid-specific secreted cysteine-rich protein (XCP1)<sup>50</sup>). Expression of resistin mRNA is tightly regulated by the nutritional status of the organism. Its inhibitory effect on the differentiation of adipocytes probably underlies its role in the feedback between the nutritional status and adipogenesis. Its quantity rises based on adipocyte differentiation and decreases after administration of insulin-sensitizing agents. Increased expression of resistin in rodents is the result of adipocyte differentiation. A higher number of adipocytes in rodents locally cause a higher production of resistin which inhibits insulin signaling and glucose uptake and thereby prevents the further differentiation of adipocytes. In this way, it probably ensures the feedback control of adipogenesis. In rodents a positive correlations have been demonstrated between an increasing level of resistin, higher levels of insulin, glucose and lipids and the development of obesity and diabetes<sup>51, 52</sup>) as well as decreased food intake and reduced thermogenesis<sup>53, 54</sup>).

Elevated plasma levels of resistin were found in connection with many inflammatory markers including CRP, soluble TNF- $\alpha$  receptor-2, IL-6 and lipoproteins in combination with phospholipase A2 under certain pathophysiological conditions<sup>55</sup>). The communication between inflammatory processes and the insulin signaling cascade allows hypothesizing that resistin may represent a key link between inflammation and its metabolic consequences following the inflammatory hypothesis of metabolic syndrome. There is a large body of preclinical evidence supporting this hypothesis<sup>25, 56, 57</sup>). In humans, however, the situation seems to be much more complicated. Resistin expression in humans occurs at a higher level in monocytes and macrophages than in adipocytes<sup>58, 59</sup>). The conclusions of numerous studies in obese individuals and patients with DM2 are contradictory as both higher and lower concentrations of resistin in plasma were found in obese individuals. Moreover, the association of plasma level of resistin or resistin gene expression in adipose tissue with BMI or insulin resistance biomarkers is not clearly confirmed<sup>60-63</sup>). It is possible that the production of resistin is secondarily increased in obesity-induced inflammatory condition of the organism and resistin alone may not contribute directly to insulin resistance.

#### **Adipocyte Fatty Acid Binding Protein (AFABP)**

Adipocyte fatty acid binding protein (AFABP) is a member of a family of mammalian intracellular fatty acid-binding proteins (FABP). AFABP involved in

transport of fatty acids can affect blood lipids, thereby influencing energy metabolism, insulin resistance and the development of atherosclerosis. Physiological functions of AFABP were further elucidated by experiments with AFABP deficient mice that were protected from hyperinsulinemia and insulin resistance after being kept on rich-fat diet. Their adipocytes had reduced the ability for lipolysis and released 2 to 3-fold less fatty acids. AFABP knock-out mice were shown to have reduced the risk of atherosclerosis and AFABP levels are positively correlated with both obesity and rich-fat diet<sup>64</sup>.

Plasma level of AFABP in humans is closely correlated with the degree of obesity and the development of insulin resistance and positively correlated with waist circumference, blood pressure values, and parameters of lipid metabolism, serum fasting insulin and insulin resistance index. AFABP levels are higher in people who have multiple components of metabolic syndrome<sup>65</sup>. Its serum levels vary among individuals with transient and permanent weight loss<sup>66</sup>. In morbidly obese patients significantly reduced plasma levels of AFABP after gastric banding weight loss were found<sup>67</sup>. Long-term observations of individuals with higher levels of AFABP have clearly worsened the prognosis and increased the cardiometabolic risk of metabolic syndrome. Based on these findings AFABP is considered to be a marker of metabolic syndrome<sup>65</sup>. It is assumed that therapeutic intervention regarding AFABP could contribute to the treatment of obesity, diabetes mellitus and atherosclerosis<sup>68–70</sup>.

#### *TNF- $\alpha$*

TNF- $\alpha$  is produced mainly by macrophages of the adipose tissue. Its autocrine activity is manifested by direct effects on the insulin signaling cascade. TNF- $\alpha$  induces the phosphorylation of the insulin receptor substrate and therefore prevents an interaction of insulin with the insulin receptor. Paracrine effects of TNF- $\alpha$  comprise an increase in the hormone-sensitive lipase activity in the adipose tissue and thus an enhancement of free fatty acids release to circulation, which then promote insulin resistance in other organs (e.g. muscle, liver tissue). In humans, some studies have demonstrated that a higher production of TNF and adipocytes and its elevated plasma levels positively correlated with the degree of obesity, insulin levels and insulin resistance<sup>25</sup>. Interestingly, the administration of TNF- $\alpha$  abolishes the insulin-sensitive effects of adiponectin and the administration of adiponectin suppresses insulin resistance induced by TNF- $\alpha$ <sup>17, 71</sup>.

#### *Interleukin-6 (IL-6)*

Interleukin-6 (IL-6) is pro-inflammatory cytokine and its main source besides the immune system cells is also the visceral adipose tissue. Its expression and secretion in obesity is enhanced and positively correlated with the parameters of insulin resistance. This effect is exerted in adipocytes and hepatocytes by inhibition of insulin signaling pathways<sup>72</sup>. Lipolytic effect of IL-6 in the adipose tissue consequently increases free fatty acids in circulation and hepatic *de novo* synthesis of fatty acids and cholesterol<sup>17, 25</sup> and was associated with obesity-related

hypertriglyceridemia by stimulating hepatic secretion of very low-density lipoprotein<sup>73</sup>. Both *in vivo* and *in vitro* human studies have shown that interleukin-6 also inhibits, together with TNF- $\alpha$ , secretion of adiponectin<sup>74</sup>.

In the human adipose tissue culture, IL-6 increased leptin secretion, reduced adiponectin secretion, increased lipolysis, and decreased lipoprotein lipase activity<sup>75</sup>. However, since IL-6 was long ago also shown to be released from the skeletal muscle immediately after exercise<sup>76</sup> and to promote fatty acid oxidation and glucose uptake in the skeletal muscle<sup>77, 78</sup>, its role in insulin resistance is still not fully elucidated.

#### *Interleukin-1 $\beta$ (IL-1 $\beta$ )*

Interleukin-1 $\beta$  (IL-1 $\beta$ ) is a pro-inflammatory cytokine produced by macrophages in the adipose tissue. IL-1 $\beta$  is involved in the development of insulin resistance by reducing the expression of insulin receptor substrate 1 (IRS-1) at the level of transcription and thus impairs the insulin signaling pathway<sup>17</sup>.

Relationships between IL-1 $\beta$  levels and metabolic syndrome components such as diabetes type 2 have also been suggested as IL-1 $\beta$  was shown to contribute to impaired insulin signaling and consequent development of insulin resistance<sup>79</sup>. Studies in adipocyte cell lines and human adipocytes chronically treated with IL-1 $\beta$  suggest that its elevated levels could result in insulin resistance and reduced lipid storage in adipocytes where IL-1 $\beta$  is up-regulated at the conditions of obesity<sup>80</sup>.

#### **Conclusion and future directions**

Metabolic syndrome represents an increasingly urgent challenge for new pharmacotherapy development. There is a growing body of data showing multiple dysregulations in adipose tissue metabolism.

Pathophysiology of the adipose tissue has received increasing attention over the past decades<sup>81</sup>.

Anatomical, cellular, molecular, physiological, clinical and prognostic differences also regarding differences in adipokine production and secretion of the visceral and subcutaneous adipose tissue have been intensively studied<sup>82</sup>.

This suggests targeting adipokines as promising candidates and a source of drugs with innovative mechanisms of action and potentially a basis for novel pharmacotherapeutic approaches. One example represents metreleptin, an analogue of leptin, an orphan drug recently approved as replacement therapy to treat the complications of leptin deficiency, in addition to diet, in patients with congenital generalized or acquired generalized lipodystrophy<sup>83, 84</sup>.

Nevertheless, the intense research has not provided yet a complete understanding of actions of adipokines. As new functions and effects of adipokines are being revealed, new questions arise on the field. For instance, recently other than purely metabolic functions of adiponectin have been identified, suggesting its deep involvement in skeletal muscle regeneration<sup>85</sup>.

This aspect in general also limits and currently prevents introducing novel adipokine-related pharmacological treatment strategies in clinical use. However, it is

necessary to point out also some other mechanisms involved in the development of metabolic syndrome.

One of the most important is the endocannabinoid system which is consistently reported to have a strong influence on appetite, metabolism and energy homeostasis<sup>86–88</sup>, and preclinical studies are constantly widening the range of new candidate molecules mostly antagonistically targeting the CB1 receptor which seems to be the most promising potential therapeutic approach<sup>89–91</sup>.

Another direction on the field of metabolic syndrome treatment is studying nuclear erythroid factor 2, a transcription factor that serves as a master regulator of the adaptive response to oxidative and electrophilic stresses<sup>92</sup> or curcumin, a phytochemical with good evidence of many effects including the anti-inflammatory, antioxidant, antithrombotic, antiatherosclerotic and cardioprotective ones, suggesting its potential usefulness in metabolic syndrome treatment<sup>93</sup>. Furthermore, there are other currently persuaded directions of metabolic syndrome research such as targeting of corticosteroid metabolism by inhibition of 11 $\beta$ -hydroxysteroid dehydrogenase type 1, an enzyme over-expressed in obese and diabetic patients which catalyzes the conversion of inactive cortisone to active cortisol, especially in the liver and adipose tissue<sup>94</sup> and therapeutic use of bioactive peptides deriving from milk proteins as a nutraceutical approach<sup>95</sup>.

In conclusion, there are currently many potential approaches identified for a future drug development for metabolic syndrome, some of them already close to the clinical stage of the development. The pharmacological exploitation of adipokines signaling pathways might provide a source of drugs with innovative mechanism of action, although there are still several important barriers on the way from the adipokine-related drug development process to the implementation of novel pharmacotherapeutic concept in the future clinical use.

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